EXHIBIT 1

Abandoned therapies and unpublished trials in rheumatoid arthritis

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The capability of selectively targeting pathogenic elements of disease with biologic therapies has created a new therapeutic repertoire. Although a substantial number of biologic agents have been developed for treatment of rheumatoid arthritis, few have been approved for use. Most of the agents have failed to reach the approval stage because of inadequate clinical benefit. Despite this, studies of these agents have provided extremely valuable lessons in study design, immunobiology, pharmacodynamic evaluation, and the utility of animal models in the development of biologic agents. These insights have laid the groundwork for future development of other novel therapeutic agents in the treatment of rheumatoid arthritis. Curr Opin Rheumatol 2003, 15:253–258

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Abbreviations

ICAM-1	intercellular adhesion molecule-1
IFN	interferon
IL	interleukin
mAb	monoclonal antibody
MMPs	matrix metalloproteinases
RA	rheumatoid arthritis
TCRs	T-cell receptors
TNF	tumor necrosis factor

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An improved understanding of the pathogenesis of rheumatoid arthritis (RA) together with recent advances in biotechnology has led to selective targeting of the pathogenic elements of disease with biologic agents [1,2•,3•]. The pathogenic elements currently considered as therapeutic targets in RA include adhesion molecules, cellular elements (T cells, B cells, and synovial lining cells), antigen-presenting cells, the major histocompatibility complex/antigen/T cell receptor (trimolecular) complex, complement costimulatory molecules, cytokines, chemokines, angiogenic molecules, and proteolytic enzymes [4,5]. Over the past 15 years, with a few exceptions these pathogenic elements have been targeted in RA. Despite the large number of agents that have been evaluated in patients over the years, few have obtained regulatory approval. Despite this, a substantial body of knowledge has been created that provide lessons for future developments in the field. The purpose of this article is to review the lessons learned from the treatments no longer in development for RA.

Adhesion molecules as therapeutic targets

Adhesion molecules expressed on endothelial cells, circulating leukocytes, and synovial cells play a critical role in the recruitment of leukocytes to inflammatory tissues cell activate and pannus invasion into cartilage and bone. One adhesion molecule, intercellular adhesion molecule-1 (ICAM-1) results in the transmigration of leukocytes through endothelial cells into tissues.

In RA, a murine IgG2 anti-ICAM-1 monoclonal antibody (mAb) was evaluated in three open-label trials. In single-dose studies in early and late RA, anti-ICAM-1 mAb appeared to have clinical benefit associated with reduced T cell reactivity [6,7]. However, repeat treatment caused significant allergic reactivity, precluding its further use [8]. Further studies with immunogenic humanized or chimeric mAb are warranted. Another approach to inhibiting ICAM-1 was the use of ICAM-1 antisense therapy: specific antisense oligodeoxynucleotide sequences designed to inhibit the translation of ICAM-1 mRNA into the encoded protein. On the basis of promising preclinical data, a randomized controlled trial of ICAM-1 oligodeoxynucleotide administered intravenously in RA patients (for 26 days) yielded only modest clinical benefit [9]. Whether longer-term dosing will be effective remains unclear.

T cells as therapeutic targets

CD4 antigen as a target

One of the first pathogenic elements to be targeted in RA was the T cell (Table 1) [10]. The prominence of activated CD4 and T cells in the synovium, the human leukocyte antigen (HLA) class II molecule association with RA, and the benefit of T cell–depleting interventions in animal models of RA combined to provide a strong rationale for targeting CD4+ T cells using murine mAbs directed at an array of different epitopes. However, the murine mAb proved to be immunogenic, precluding their further use in RA. Subsequently, chimeric mAb were developed that constituted a constant region of a human antibody fused to the murine variable (Fab) regions. Further reduction in immunogenicity was accomplished with "humanized" mAb constituting only the hypervariable region of the murine antibody. Between 1989 and 1994, eight open-label studies were conducted with extremely promising results in 60 to 75% of patients [11]. Subsequent randomized placebo-controlled trials of both murine and chimeric anti-CD4 mAb (CMT 412) demonstrated no clinical efficacy [12,13•,14]. According to Epstein [15•], the results reflected more of an expectation bias on the part of the investigator and patient than a placebo effect. He reasoned that the reduced clinical benefit observed in the experimental group compared with the open-label trials could be accounted for by expectation bias because a true placebo effect would have resulted in similar clinical responses between the groups. The discrepant results between open-label and placebo-controlled trials emphasized the degree to which expectation biases can affect the results. Subsequent studies, even early phase I/II trials, have included a placebo arm to reduce unrealistic overenthusiastic responses to early data.

The lack of clinical benefit with T cell depletion in RA was consistent with data from rodent models of arthritis. Thus, in collagen-induced arthritis, virtual T cell depletion was needed to yield clinical benefit, thus emphasizing the trivial numbers of CD4+ T cells capable of generating an inflammatory response. Support for this concept was also shown with a study demonstrating that a single CD4+ T cell could generate a delayed hypersensitivity response. Of note, anti-CD4 mAb depletion was shown to be effective in adjuvant arthritis in rats, which pointed out the limitations of animal models.

Table 1. T cells as therapeutic targets

CD4 antigen
Depleting mAb
Murine anti-CD4
Chimeric anti-CD4 (CMT 412)
Nondepleting mAb
Primitized IgG1 anti-CD4
Humanized anti-CD4
IgG1 (4162W94)
IgG4 (Oktcdr4a)
Other T cell antigens
CD52 - CAMPATH-1H mAb
CD5 - anti-CD5 ricen toxin
IL-2R - Diphtheria IL-2 fusion protein

The pharmacodynamic effects of anti-CD4 mAbs on CD4+ T cell survival have been instructive. In contrast to murine anti-CD4+ T cell depletion (hours to several months), chimeric anti-CD4 and humanized anti-CDW 52 (Campath 1H) resulted in profound and prolonged depletion of peripheral blood CD4+ T cells for as long as 7 years [13•,16,17]. Subsequent examination of the synovial compartment revealed a lack of correlation between the reduction in the inflammatory cell infiltrate observed with the chimeric anti-CD4 mAb and clinical improvement [17]. The discrepancy was explained by the inadequate reduction of synovial CD4+ T cells and persistence of tumor necrosis factor (TNF)-α and IL-1β in the joint tissues. Of even greater significance was the persistent synovial infiltrate by CD4+ T cells at a time when there was a profound peripheral T cell depletion with campath-1H (anti-CDW 52) [18••]. In contrast to these data, a correlation between the clinical response and proportion of anti-CD4 mAb coated CD4 T cells was demonstrated in the synovial fluid of RA patients [19•]. The results suggest that inadequate dosing for the duration of therapy accounted for the lack of clinical benefit with the anti-CD4+ T cell therapy. The data also emphasize the critical importance of the synovium as a pharmacogenetic window.

The prolonged T cell depletion observed with chimeric/humanized mAb is also consistent with previous murine data. Thus, whereas short-term depletion of CD4+ T cells was observed with an anti-CD4 mAb in young mice (comparable with the age of mice traditionally used in rodent models of arthritis), prolonged depletion of CD4+ T cells was observed in older mice of an age comparable with that of mAb treated mice. In vitro murine data have shown more T cell cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and apoptosis with chimeric anti-mAb than in a heterologous counterpart. Thus, studies of chimeric mAb in animal models of RA appear to reflect the human situation more accurately, and may have predicted the prolonged depletion of T cells with the mAb in RA. The data clearly emphasize the need for preclinical studies to more closely approximate to the human therapeutic paradigm.

Several other factors may have contributed to the lack of clinical benefit of anti-CD4+ mAb. Recent evidence suggests that the duration of the therapy may not have been long enough. Thus, in the systemic lupus murine model, only prolonged treatment with an anti-CD4 mAb could prevent the development of disease [20••]. The lack of clinical benefit may also reflect the resistance of pathogenic memory CD4 T cells to anti-CD4 mAb treatment. Whether nonselective CD4 T cell depletion results in

immune dysregulation as a consequence of differential effects on T-helper and T-suppressor cell function remains unclear.

The clinical consequence of prolonged peripheral blood T cell depletion with anti-CD4 mAb has been particularly instructive. Thus, despite prolonged CD4+ T cell depletion to levels observed in patients with human immunodeficiency virus infection, few patients experienced sepsis or opportunistic infections. This likely reflects the inability of the mAb to deplete CD4 T cells from lymphoid tissues. Whether patients with prolonged peripheral CD4 T cell depletion from mAbs will be more susceptible to infection with other immunomodulatory agents remains unclear.

The failure of depleting mAbs to demonstrate clinical benefit may also be accounted for by their inability to adequately modulate T cell function. Thus, animal models showed that the effectiveness of anti-CD4 mAb was not dependent on depletion of T cells [20••]. Rather, modulation of T cell function (without depletion) appeared critical. This concept is supported by the apparent correlation between the anti-CD4 mAb coating of RA synovial fluid cells and the clinical benefit [19•]. As a consequence of these and other data, an alternative approach using nondepleting anti-CD4 mAb was subsequently used in the treatment of RA.

Initial studies with nondepleting anti-CD4 mAb were carried out with a primate derived (primitized) and humanized IgG4 mAb. Preliminary data from open label studies demonstrated only transient reduction of CD4+ T cells with suggestive clinical benefit. The first randomized controlled trial performed with the primitized mAb demonstrated good clinical responses [21••]. However, a second randomized controlled trial performed with the primitized antibody generated by a different manufacturing process yielded significant reduced efficacy and peripheral blood CD4 T cell depletion, resulting in discontinuation of development. Although both antibodies were generated in Chinese hamster ovary cell lines, differences in the level of aggregation and nonglycosylated heavy chain might have accounted for the results [22••]. Of significance, the clinical response was correlated with CD4+ T cell coating but not CD4 T cell depletion. The humanized IgG1 mAb (4162W94) resulted in significant peripheral CD4+ T cell coating, which correlated with clinical improvement in an open-label study [23]. A subsequent randomized controlled trial was carried out, but the agent was also discontinued from further development. The humanized IgG4 anti-CD4 mAb (OCTcdr4a) was evaluated in a small randomized controlled trial that demonstrated good clinical efficacy without CD4 T cell depletion; however, development was discontinued. More recently, other humanized (Humax CD4) nondepleting anti-CD4 mAb was evaluated in RA. A phase II randomized controlled trial, however, demonstrated no clinical benefit after 4 weeks of treatment.

Other T cell antigens as targets

Several other T cell antigens have been targets for therapy, including CD52, CD5, and IL-2 receptor. CAMPATH-1H ab humanized IgG1 mAb directed against CD52 (a lymphocyte antigen) was evaluated in several studies in RA [24–26]. Although significant improvement was demonstrated, profound and prolonged CD4 T cell depletion was observed. As a consequence, CAMPATH-1H is no longer in development. Another antigen on all T cells, CD5, was targeted with a murine IgG1 anti-CD5 mAb linked to a Ricin A chain, a plant toxin that blocks protein synthesis. Despite encouraging results in open-label trials associated with depletion of peripheral T cells, no clinical benefit was observed in a randomized controlled trial [27]. CD25 (IL-2 receptor antigen), which is expressed on activated but not resting T cells, has also been targeted using mAb to the IL-2 receptor and IL-2 linked to a diphtheria toxin. DAB 486 IL-2, a fusion protein comprising IL-2 and a diphtheria toxin fragment, results in the inhibition of protein synthesis and cell death shortly after internalization in the cell. In phase II randomized controlled trials of DAB 486 Il-2 and a similar (but shorter) compound, no clinical benefit was observed [28].

The trimolecular complex as a therapeutic target

Major histocompatibility complex

The DR4-DR1 peptides were developed for RA to generate anti-DR4/DR1 antibodies, thereby interfering with the trimolecular complex (Table 2). A phase I/II randomized controlled trial involving DR4/DR1 peptide immunization yielded only modest clinical benefit: anti-DR4/DR1 antibodies were detected in 25% of patients [29].

T-cell receptor

Because recent data suggested overexpression of specific T-cell receptors (TCRs) (VB3, 14, and 17) in RA, TCR peptide immunization with a combination of VB3, 14, and 17 TCR peptides was carried out in a randomized controlled trial in RA patients [30,31]. A modest clinical benefit was observed in the total RA population studied,

Table 2. Trimolecular complex as a target

MHC complex
DR4/DR1 peptic vaccine
T cell receptor
VB3, 14, 17 TcR peptide vaccine
Putative autoantigens
Collagen
Chicken
Bovine
Human cartilage (HC) gp 39

whereas patients who had had RA less than 3 years, or who received less than 7.5 mg/day prednisone, showed greater benefit [32•].

Putative autoantigens

Oral tolerance—antigen-specific hyporesponsiveness as a consequence of proteins passing through the gut—has been examined with several autoantigens. Initial studies with oral chicken collagen in a randomized controlled trial demonstrated clinical benefit, but subsequent randomized controlled trials using either chicken collagen or bovine collagen demonstrated little benefit [33]. More recently, human cartilage glycoprotein 39 (HC gp39) was identified as a possible candidate autoantigen in RA based on the amelioration of collagen induced arthritis, both clinically and radiographically, with intranasal administration of HCgp-39 [34,35]. Although the initial studies in patients with RA were encouraging, the results of subsequent trials suggested that further development was not warranted.

Cytokines as therapeutic targets

Several cytokines are useful as therapeutic targets (Table 3).

Tumor necrosis factor

Tumor necrosis factor has proved to be a pivotal cytokine in the pathogenesis of RA. One early approach to targeting TNF was the development of a recombinant fusion protein comprising two extracellular domains of the human p55 kDa TNF receptor and an Ig2, heavy chain. This agent, RO45–2081 (lenercept), was administered intravenously and then subcutaneously in several studies [36–39]. Although apparent clinical benefit was observed, lenercept given weekly subcutaneously resulted in the generation of antilenercept antibodies that accelerated clearing with repeat dosing, although no correlation was observed between efficacy and antilenercept antibodies. Clinical development has been discontinued.

Cytokine antagonists: interleukin-4 and interleukin-10

Interleukin (IL)-4 and IL-10 are capable of suppressing T_H1-driven proinflammatory cytokines. A substantial amount of preclinical animal model data generated with soluble cytokines or gene therapy demonstrated significant amelioration of disease. The lack of IL-4 in RA synovium provided an additional stimulus for investigation of this cytokine. Moreover, the combination of IL-4 with IL-10 had an additive effect, inhibiting cartilage degradation. Several studies evaluating recombinant human IL-10 (rhu IL-10) in RA have been carried out. Although an early phase I randomized controlled trial suggested trends to clinical improvement as well as pharmacodynamic effects, subsequent studies demonstrated little significant benefit [40]. A phase I randomized controlled trial of recombinant rhu IL-4 also failed to show significant clinical efficacy [41].

Table 3. Cytokines as therapeutic targets

TNF
sTNFR: P55 (Lenercept)
IL-4 mAb
IL-10 mAb
IL-11 mAb
IL-12 mAb
Interferons
Interferon δ
Interferon β-1b

Interleukin-11

Interleukin-11 has been shown to reduce the production of nitric oxide and proinflammatory cytokines. As a consequence, recombinant human IL-11 was evaluated in a phase I/II study in RA. At the doses examined, only marginal clinical benefit was achieved [42].

Interleukin-8

Interleukin-8 is a proinflammatory member of the CXC family of chemokines, which increases neutrophil infiltration and activation as well as promoting angiogenesis. A fully human mAb generated using XenoMouse technology was evaluated in RA. A phase IIa trial in RA of the anti-IL-8 mAb administered intravenously every 3 weeks for a total of four infusions demonstrated no significant clinical benefit.

Interferon

Interferon (IFN) has antiviral and antiproliferative properties. Several forms also have immunomodulatory activity. IFNδ in several randomized controlled trials has generally shown minimal clinical benefit [43–52]. Recombinant IFNβ-1b demonstrated no clinical benefit in a phase II placebo-controlled trial despite preliminary pilot trial data, suggesting some efficacy [53].

Matrix metalloproteinase inhibitors

Because matrix metalloproteinases (MMPs) such as collagenases, stromelysins gelatinases, and membrane-type MMPs have a critical role in cartilage and bone destruction in RA, they are considered ideal targets for therapeutic intervention. Several broad-spectrum MMP inhibitors have been developed for inhibiting metastases and angiogenesis. One of these broad-spectrum inhibitors, marinastat (BB2516), demonstrated drug-related toxicity of musculoskeletal pain and stiffness of the hands. The toxicity was dose dependent and reversible with drug withdrawal [54].

Bay 12–9566, an oral broad-spectrum MMP inhibitor capable of inhibiting both stromelysin and gelatinase, was used in trials of osteoarthritis but was discontinued. Ro113 0830, an MMP inhibitor with activity against collagenase 2 and 3, was halted in phase II trials of OA. Ro-32–3555 (Trocade) was shown to be selective for col-

lagenases 1, 2, and 3 [54]. Efficacy was demonstrated in several preclinical models of arthritis. Phase III clinical trials in RA were halted because of lack of efficacy in inhibiting radiographic progression.

Conclusion

A significant number of agents have been developed to specifically target the pathogenic elements of disease in RA. Despite the failure in developing most of these agents, they have provided substantial insight into study design, immunobiology, pharmacodynamics, and safety issues related to biologic therapy. These agents provide the foundation on which more efficacious therapies will be generated.

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